

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 September 2002 (26.09.2002)

PCT

(10) International Publication Number
WO 02/074173 A1

(51) International Patent Classification⁷: A61B 17/20, B05D 1/18, 1/28 (74) Agents: MILLER, D., Byron et al.; 1900 Charleston Road, M10-3, P.O. Box 7210, Mountain View, CA 94039-7210 (US).

(21) International Application Number: PCT/US02/07674

(22) International Filing Date: 15 March 2002 (15.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/276,762 16 March 2001 (16.03.2001) US
60/342,550 20 December 2001 (20.12.2001) US
60/351,586 22 January 2002 (22.01.2002) US

(71) Applicant: ALZA CORPORATION [US/US]; 1900 Charleston Road, M10-3, P.O. Box 7210, Mountain View, CA 94039-7210 (US).

(72) Inventors: TRAUTMAN, D., Byron; 1574 Wright Avenue, Sunnyvale, CA 94087 (US). WRIGHT, Cedric, T.; 795 Hilmar Street, Santa Clara, CA 95050 (US). CORMIER, Michel, J., N.; 278 Andsbury Avenue, Mountain View, CA 94043 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARPO patent (GI, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

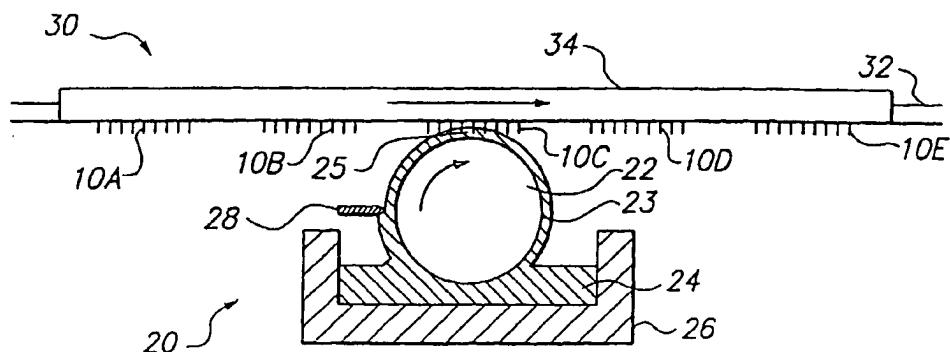
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

[Continued on next page]

(54) Title: METHOD AND APPARATUS FOR COATING SKIN PIERCING MICROPROJECTIONS



WO 02/074173 A1



(57) Abstract: An apparatus and method are provided for selectively applying an agent-containing liquid coating to extremely tiny skin piercing microprojections (10). The coating solution is applied to the skin piercing microprojections (10) using a coating technique which selectively coats only the skin piercing microprojections (10) and not the substrate (12) from which the microprojections (10) extend, and then dried. The coating method includes providing an agent-containing coating liquid and conveying the liquid to a liquid holding surface having a coating transfer region. The depth of the coating liquid at the coating transfer region is precisely controlled. The microprojections are then immersed to a predetermined level in the coating liquid. The liquid that coats the microprojections (10) is then dried to form a solid agent-containing coating on the microprojections (10).



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

METHOD AND APPARATUS FOR COATING
SKIN PIERCING MICROPROJECTIONS

CROSS REFERENCE TO RELATED APPLICATIONS

5

[0001] Priority is claimed from U.S. Patent Applications Serial Nos. 60/276,762 filed March 16, 2001; 60/342,550 filed December 20, 2001; and 60/351,586 filed January 22, 2002.

10

TECHNICAL FIELD

[0002] This invention relates to administering and enhancing delivery of an agent into or through the skin. More particularly, the invention relates to a method and apparatus for making a percutaneous drug delivery system for 15 administering therapeutic active agent (i.e., a drug or vaccine) into or through the skin using skin piercing microprojections which have a dry coating of the agent. Delivery of the agent is facilitated when the microprojections pierce the skin of a patient and the patient's body fluid contacts and dissolves the active agent. Even more particularly, the invention relates to a method and apparatus 20 for selectively coating the agent on the microprojections.

BACKGROUND ART

[0003] Transdermal drug delivery systems generally rely on passive diffusion 25 to administer the drug while active transdermal drug delivery systems rely on an external energy source (e.g., electricity) to deliver the drug. Passive transdermal drug delivery systems are more common. Passive transdermal systems have a drug reservoir containing a high concentration of drug adapted to contact the skin where the drug diffuses through the skin and into the body tissues or 30 bloodstream of a patient. The transdermal drug flux is dependent upon the condition of the skin, the size and physical/chemical properties of the drug molecule, and the concentration gradient across the skin. Because of the low skin permeability to many drugs, transdermal delivery has had limited

applications. This low permeability is attributed primarily to the stratum corneum, the outermost skin layer which consists of flat, dead cells filled with keratin fibers (keratinocytes) surrounded by lipid bilayers. The highly-ordered structure of the lipid bilayers confers a relatively impermeable character to the stratum corneum.

5

[0004] One method of increasing the passive transdermal diffusional drug flux involves mechanically penetrating or disrupting the outermost skin layers thereby creating pathways into the skin in order to enhance the amount of agent being transdermally delivered. Early vaccination devices known as scarifiers generally 10 had a plurality of tines or needles which are applied to the skin to and scratch or make small cuts in the area of application. The vaccine was applied either topically on the skin, as disclosed in Rabenau, U.S. Patent 5,487,726 or as a wetted liquid applied to the scarifier tines as disclosed in Galy, U.S. Patent 4,453,926, Chacornac, U.S. Patent 4,109,655, and Kravitz, U.S. Patent 15 3,136,314 or as a dry coating on and between the scarifier tines as disclosed in Kravitz US Patent 3,351,059. Scarifiers have been suggested for intradermal vaccine delivery in part because only very small amounts of the vaccine need to be delivered into the skin to be effective in immunizing the patient. Further, the amount of vaccine delivered is not particularly critical since an excess amount 20 achieves satisfactory immunization as well as a minimum amount. However a serious disadvantage in using a scarifier to deliver a drug is the difficulty in determining the transdermal drug flux and the resulting dosage delivered. Also due to the elastic, deforming and resilient nature of skin to deflect and resist puncturing, very tiny (e.g., having lengths less than about 0.5 mm) skin piercing 25 elements often do not uniformly penetrate the skin and/or are wiped free of a coating, particularly a liquid coating, of an agent upon skin penetration. Additionally, due to the self healing process of the skin, the punctures or slits made in the skin tend to close up after removal of the piercing elements from the stratum corneum. Thus, the elastic nature of the skin acts to remove active 30 agent coating the tiny piercing elements upon penetration. Furthermore the tiny slits formed by the piercing elements heal quickly after removal of the device,

thus, limiting the passage of agent through the passageways created by the piercing elements and in turn limiting the transdermal flux of such devices.

[0005] Other devices which use tiny skin piercing elements to enhance transdermal drug delivery are disclosed in European Patent EP 0407063A1, Godshall, et al. US Patent 5,879,326; Ganderton, et al. US Patent 3,814,097; Gross, et al. US Patent 5,279,544; Lee, et al. US Patent 5,250,023; Gerstel, et al. US Patent 3,964,482; Kravitz, et al. US Patent Reissue 25,637 and PCT Publication Nos. WO 96/37155, WO 96/37256, WO 96/17648, WO 97/03718, WO 98/11937, WO 98/00193, WO 97/48440, WO 97/48441, WO 97/48442, WO 98/00193, WO 99/64580, WO 98/28037, WO 98/29298, and WO 98/29365.

These devices use piercing elements of various shapes and sizes to pierce the outermost layer (i.e., the stratum corneum) of the skin. The piercing elements disclosed in these references generally extend perpendicularly from a thin, flat member, such as a pad or sheet. The piercing elements in some of these devices are extremely small, some having dimensions (i.e., a microprojection length and width) of only about 25 - 400 μm and a microprojection thickness of only about 5 - 50 μm . These tiny piercing/cutting elements make correspondingly small microslits/microcuts in the stratum corneum for enhanced transdermal agent delivery therethrough.

[0006] More recently, Cormier et al., in US Patent Application Serial No. 60/244,038 filed October 26, 2000 disclose a device for transdermally delivering a potent drug. The device has a plurality of skin piercing microprojections which have a dry coating of the drug. Cormier et al. disclose microfluidic coating techniques such as ink jet printing to selectively coat the drug only on the skin piercing microprojections rather than on other portions/surfaces of the device which do not penetrate into the skin. In spite of these disclosures, Cormier et al. do not address the difficulties in aiming the microfluidic spray or deposit only onto the portions of the device which pierce the skin. Thus, there is a need for a precisely controlled coating method which can reproducibly, and at high volumes, coat only the skin-piercing portions of such devices.

DISCLOSURE OF THE INVENTION

[0007] The apparatus and method of the present invention overcome these difficulties by providing a coating liquid of precisely controlled depth and conveying, in a precisely controlled manner the microprojections through the coating liquid. The method of the present invention is useful for coating a liquid onto a plurality of microprojections extending from a surface or edge of a substrate without coating the liquid onto the substrate itself. The method includes providing an agent-containing coating liquid and conveying the liquid onto a liquid-holding surface having a coating transfer region. The depth of the coating liquid on the coating transfer region is precisely controlled to a predetermined depth. The microprojections are immersed to a predetermined level in the coating liquid at the coating transfer region. The depth of the coating liquid in the coating transfer region should be at least slightly greater than the level of immersion of the microprojections, as measured perpendicularly from the substrate surface or edge. The microprojections are most typically immersed only partially in the coating liquid so that only a portion of the entire length of the microprojections is coated. After coating, the microprojections are removed from the coating liquid and then dried thereby forming a dry agent-containing coating on the microprojections. An important advantage of the present invention is that for very expensive agents (e.g., expensive drugs or vaccines), the agent is coated only on those portions of the device which pierce into the skin, i.e., only the microprojections and not the substrate is coated with the agent.

25

[0008] The apparatus of the present invention is suitable for coating an agent-containing liquid onto a plurality of microprojections extending from a surface or edge of a substrate substantially without coating the substrate. The apparatus includes a liquid holding surface having a coating transfer region. The liquid holding surface can be either curved or flat. A liquid conveyor conveys the coating liquid to the coating transfer region. A coating thickness controller controls the thickness of the coating at the coating transfer region to a precisely

predetermined thickness. A positionably adjustable substrate conveyer conveys the microprojections past the coating transfer region such that the microprojections are immersed to a predetermined depth level in the coating liquid.

5

[0009] In one embodiment, the liquid holding surface is the cylindrically-shaped outer surface of a rotatable roller or drum. The coating liquid is conveyed to a coating transfer region by rotating the roller or drum through a bath of the coating liquid. The coating thickness controller can be either a doctor 10 blade and/or a second roller substantially parallel with the liquid conveying roller or drum and spaced a predetermined distance therefrom.

[00010] In a second embodiment, the liquid holding surface, either curved or flat, is substantially immobile and the coating liquid flows e.g., by force of 15 gravity, thereover.

[00011] The substrate conveyer can take any of several forms. In one embodiment, the substrate conveyer comprises a track which is positionally adjustable relative to the coating transfer region. A substrate holding sled runs 20 along the track past the coating transfer region.

[00012] In a second embodiment, the substrate conveyer continuously conveys a web comprised of a plurality of substrates past the coating transfer region. The continuous substrate conveyer can include a substrate web supply 25 roll and a take-up roll with a positionally adjustable web guide therebetween for positioning the continuous web relative to the coating transfer region.

[00013] Preferably, the agent is sufficiently potent to be therapeutically effective in a dose of less than about 1 mg, and preferably less than about 0.25 30 mg, per application. Preferably, the agent has a water solubility of greater than about 50 mg/ml, and more preferably greater than about 100 mg/ml. The liquid coating solution or suspension typically has a viscosity of about 5 to 500

centipoise (cP), more typically about 20 to 50 cP, when measured at a temperature of 25°C and a shear strain rate of 100 sec⁻¹. The thickness of the solid (i.e., after drying) coating on the microprojections is preferably less than the thickness of the microprojections, more preferably the thickness is less than 25 5 μm and most preferably less than 10 μm . Generally, the coating thickness is an average thickness measured over the surfaces of the microprojections.

[00014] The agent for coating the microprojections is selected to have sufficient potency to be therapeutically effective when administered 10 transdermally in an amount of less than about 1 mg, and preferably less than about 0.25 mg, of active agent. The most preferred agents are vaccines and potent drugs. Preferred potent drugs include ACTH (1-24), calcitonin, desmopressin, LHRH, LHRH analogs, goserelin, leuprolide, PTH, vasopressin, deamino [Val4, D-Arg8] arginine vasopressin, buserelin, triptorelin, interferon 15 alpha, interferon beta, interferon gamma, FSH, EPO, GM-CSF, G-CSF, IL-10, glucagon and analogs of these agents including pharmaceutically acceptable salts thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

20 [00015] The invention will now be described in greater detail with reference to the preferred embodiments illustrated in the accompanying drawings and figures, wherein:

25 [00016] FIG. 1 is a perspective view of a portion of one example of a microprojection array;

[00017] FIG. 2 is a perspective view of the microprojection array of FIG. 1 with a coating deposited onto the microprojections;

30 [00018] FIG. 3 is a side schematic view of one embodiment of the apparatus according to the present invention;

[00019] FIG. 4 is a side schematic view of another apparatus according to the present invention;

5 [00020] FIG. 5 is a side schematic view of yet another apparatus according to the present invention;

[00021] FIG. 6 is a side perspective view showing a continuous substrate conveyor in accordance with one embodiment of the present invention;

10

[00022] FIG. 7 is a side view, shown partly in section, of a portion of the coating apparatus of the present invention;

15

[00023] FIG. 8 is a side sectional view of an intradermal agent delivery system having a microprojection member with microprojections which are coated using the present invention;

[00024] FIG. 9 is a side sectional view of another coating apparatus of the present invention;

20

[00025] FIG. 10 is an end sectional view of the apparatus shown in FIG. 9;

25

[00026] FIG. 11 is a side view, shown partly in section, of another apparatus according to the present invention; and

[00027] FIG. 12 is a side view of the anilox roller 134 shown in FIG. 11;

30

[00028] FIG. 13 is a side schematic view of another embodiment of the apparatus of the invention;

[00029] FIG. 14 is a graph of sucrose concentration versus time during coating at varying temperature and humidity conditions;

[00030] FIG. 15 is a graph of amount of sucrose coated on microprojection arrays at varying temperature and humidity conditions;

5 [00031] FIG. 16 is a graph of sucrose concentration versus time showing the effect of water infusion during coating at ambient temperature;

[00032] FIG. 17 is a graph showing the amounts of human growth hormone coated on microprojection arrays using single and multiple coatings;

10

[00033] FIG. 18 is a graph showing the amounts of ovalbumin coated on microprojection arrays using single and multiple coatings; and

15 [00034] FIG. 19 is a graph showing amounts of GRF analog coated on microprojection arrays using multiple coatings and varying coating cycles.

MODES FOR CARRYING OUT THE INVENTION

20 [00035] The term "transdermal" means the delivery of an agent (e.g., a drug or vaccine) into and/or through the skin for local or systemic therapy.

[00036] The term "transdermal flux" means the rate of transdermal delivery.

25 [00037] The term "microprojections" refers to piercing elements which are adapted to pierce or cut through the stratum corneum into the underlying epidermis layer, or epidermis and dermis layers, of the skin of a living animal, particularly a human. The piercing elements should not pierce the skin to a depth which causes bleeding. Typically the piercing elements have a blade length of less than 500 μm , and preferably less than 250 μm . The 30 microprojections typically have a width of about 75 to 500 μm and a thickness of about 5 to 50 μm . The microprojections may be formed in different shapes, such as needles, hollow needles, blades, pins, punches, and combinations thereof.

[00038] The term "microprojection array" as used herein refers to a plurality of microprojections arranged in an array for piercing the stratum corneum. The microprojection array may be formed by etching or punching a plurality of 5 microprojections from a thin sheet and folding or bending the microprojections out of the plane of the sheet to form a configuration such as that shown in FIG. 1. The microprojection array may also be formed in other known manners, such as by forming one or more strips having microprojections along an edge of each of the strip(s) as disclosed in Zuck, US Patent 6,050,988. The microprojection 10 array may include hollow needles which hold a dry pharmacologically active agent.

[00039] The present invention provides an apparatus and method for selectively applying an agent-containing liquid on the skin piercing portions of a 15 microprojection device having a plurality of stratum corneum-piercing microprojections extending therefrom in order to form an agent-containing coating on the microprojections. The liquid-coated microprojections are then dried to form a solid coating thereon which contains the agent. The microprojections are adapted to pierce through the stratum corneum into the 20 underlying epidermis layer, or epidermis and dermis layers, but do not penetrate so deep as to reach the capillary beds and cause significant bleeding. Typically, the microprojections have a length which allows skin penetration to a depth of up to about 500 μm , and preferably up to about 400 μm . Upon piercing the stratum corneum layer of the skin, the agent-containing coating is dissolved by body fluid 25 (intracellular fluids and extracellular fluids such as interstitial fluid, blood, or mixtures thereof) and released into the skin for local or systemic therapy.

[00040] FIG. 1 illustrates one embodiment of stratum corneum-piercing microprojection member 10 for use with the present invention. FIG. 1 shows a 30 portion of the member 10 having a plurality of microprojections 12. The microprojections 12 extend at substantially a 90° angle from a sheet 14 having openings 16. The member 10 may be incorporated in an agent delivery or

sampling system 80 (shown in FIG. 8) including a backing 82 and adhesive 84 for adhering the system 80 to the skin. In the embodiment of the micropojection member 10 shown in FIGS 1, 2 and 8, the microprojections 12 are formed by etching or punching a plurality of microprojections 12 from a thin metal sheet 14 and bending the microprojections 12 out of a plane of the sheet. Metals such as stainless steel and titanium are preferred. Metal micropojection members and methods of making same are disclosed in Trautman et al, U.S. Patent 6,083,196; Zuck U.S. Patent 6,050,988; and Daddona et al., U.S. Patent 6,091,975. Other micropojection members that can be used with the present invention are formed by etching silicon using silicon chip etching techniques or by molding plastic using etched micro-molds. Silicon and plastic micropojection members are disclosed in Godshall et al. U.S. Patent 5,879,326.

[00041] FIG. 2 illustrates the micropojection member 10 having microprojections 12 having a pharmacologically active agent-containing coating 18. The coating 18 may partially or completely cover the microprojections 12.

[00042] In accordance with the present invention, the agent-containing coating is applied after the microprojections 12 are formed (i.e., etched) and bent out of the plane of metal sheet 14. The coating on the microprojections 12 is formed by a dip-coating using the apparatuses shown in FIGS. 3 through 7, 9 and 10. FIG. 3 discloses one embodiment of a micropojection member coating apparatus 20 in accordance with the present invention. Coating apparatus 20 includes a rotating drum 22 partially immersed in a bath of coating liquid 24. The coating liquid 24 is contained within open container 26. Drum 22 rotates in a clockwise manner as shown by the arrow. The liquid 24 is picked up by the surface of the rotating drum as it rotates through the bath. A doctor blade 28 is provided to control the thickness of the coating liquid downstream from the doctor blade. Thus, the outer surface 23 of the rotating drum acts as a coating liquid holding surface which transfers the coating liquid to the coating transfer region 25 located at approximately the 12 o'clock position of the rotating drum 22.

[00043] The material used for the drum 22, or any surface treatment thereof, will be somewhat dependent on the particular liquid 24 being coated. Those skilled in the art will appreciate that the coating liquid must be able to wet the surface of drum 22. For aqueous protein coating solutions, a drum made of 5 Delrin®, an acetal resin sold by E.I. DuPont de Nemours and Co. of Wilmington, DE has been found to work well.

[00044] Similarly, the drum surface speed (i.e., the circumference of the 10 drum multiplied by the drum rotational speed) will also be somewhat dependent upon the particular liquid 24 being coated. Drum surface speeds of about 20 to 150 cm/minute (10 to 60 inches/minute) are typically used, while drum speeds of 50 to 75 cm/minute (20 to 30 inches/minute) have been found to be most useful for coating aqueous protein solutions.

15 [00045] Positioned above the rotating drum 22 is a microprojection member conveyor 30. Conveyor 30 includes a track 32 on which rides one or more sleds 34. Sled 34 has a plurality of microprojection members 10a, 10b, 10c, 10d, and 10e mounted thereon. The position of the track 32 relative to the top of the 20 rotating drum 22 is precisely controlled using micrometer-like position adjusting elements (not shown in FIG. 3). The sled 34 is adapted to move on track 32 from left to right as shown by the arrow. As the microprojection members 10e, 10d, and 10c pass over the rotating drum 22, the microprojections are coated by the coating liquid 24 in the coating transfer region 25. Preferably the rotational 25 speed of drum 22 is controlled so that the speed of the outer surface of drum 22 approximately matches the speed of sled 34 moving along track 32. In this way, there is essentially no wake created in the coating transfer region 25 by the microprojection members 10 moving through region 25. This is important in preventing any ripples/waves in the surface of the coating liquid in the coating 30 transfer region 25 which could otherwise cause coating of the sheet 14 (see FIG. 1) of the microprojection members 10 or a difference in coating length between the upstream and downstream sides of the microprojections.

[00046] Fig. 4 and 6 illustrate an alternate microprojection member conveyor 40. In this embodiment, the microprojection members 10a, 10b, and 10c are part of a continuous web 42. The web 42 is fed continuously under anvil 44 which, like track 32, is precisely positionable with respect to the outer surface of the rotating drum 22. In a more preferred embodiment, the microprojection member web conveyor 40 may include a web supply roll 46 and a web take-up roll 48 as shown in FIG. 6. The microprojections may optionally be punched (i.e., bent) out of the plane of the web 42 at a punching station (not shown in FIG. 6) positioned between the supply roll 46 and the anvil 44. Optionally, the coated individual microprojection members 10 can be punched out of web 42 downstream of anvil 44 and before takeup of the excess web on take-up roll 48.

[00047] The microprojection member coating apparatus 50 shown in FIG. 5 is similar to the coating apparatus shown in FIG. 4 with the following differences. The rotating coating drum 52 has a coating thickness controller in the form of a parallel secondary roller 54 spaced a predetermined distance therefrom. A wiping blade 56 wipes the surface of secondary roller 54 so that the surface of roller 54 is substantially liquid free as it enters the nip between the rotating drum 52 and the secondary roller 54. In this manner, a coating liquid of precisely controlled thickness is provided on the surface of rotating drum 52 upstream from the nip between secondary roller 54 and drum 52. In this manner, the thickness of the coating liquid in the coating transfer region 25 is precisely controlled. A microprojection member conveyor including an adjustably positionable anvil 44 and a continuous web of microprojection members 42 is conveyed past the coating transfer region 25 in the direction of the arrows. Thus, the direction of web 42 is substantially the same as the rotational direction of rotating drum 52 with the speeds thereof roughly matched in order to prevent waves and ripples in the coating liquid in region 25.

30

[00048] FIG. 13 discloses an alternate microprojection member coating apparatus 80 similar to the apparatus shown in FIG. 5 but having a different

micropromtrusion member conveyor. The micropromtrusion member conveyor of apparatus 80 comprises a drum 82 having removably mounted thereon a plurality of micropromtrusion members 10. The mounting of members 10 on the cylindrical surface of drum 82 can be done by conventional means, including 5 having a hollow drum 82 with small openings on the cylindrical surface through which a partial vacuum is drawn, using magnets (in the case of ferro metallic members 10) and other known non-permanent mounting means. Drum 82 is adapted to rotate around axis 84 as shown by the arrow. As drum 82 rotates about axis 84, the micropromtrusions of members 10 are sequentially conveyed 10 through coating transfer region 25. The depth of the coating liquid 24 in coating transfer region 25 is controlled as is previously described in connection with the apparatus 50 of FIG. 5. This apparatus enables the micropromtrusion members to be coated multiple times without operator intervention. Although FIG. 13 shows a cylindrically shaped drum 82 having the micropromtrusion members 10 mounted 15 thereon, those skilled in the art will appreciate that only a partial cylindrical surface is necessary in order to coat according to the method illustrated in FIG. 13.

[00049] FIG. 7 discloses an alternate micropromtrusion member coating apparatus 70 comprised of a container 76 holding the coating liquid 74. A pump 72 is provided to pump the coating liquid 74 through conduit 78. Upon emerging from conduit 78, the thickness of the coating liquid is controlled using a secondary roller 77 and doctor blade 79 similar to that shown in FIG. 5. The coating liquid then flows downwardly over inclined liquid holding surface 73 to 25 the coating transfer region 75. An appropriate micropromtrusion member conveying means (not shown in FIG. 7) conveys the web 42 of micropromtrusion members 10 parallel to surface 43 whereby the micropromtrusions are coated with the coating liquid. In this embodiment, the liquid holding surface is stationary rather than moving as shown in the FIG. 3-6 embodiments.

30

[00050] FIGS. 9 and 10 disclose an alternate coating apparatus according to the present invention. The coating apparatus disclosed in FIGS. 9 and 10 is

similar to that disclosed in FIGS. 3-5 except that the cylindrically shaped coating drum has a plurality of grooves 129 therein. The coating liquid 124 is carried within the grooves of the rotating drum 122 as best shown in FIG. 10. The micropojection member 110 having a plurality of micropojections 112 is 5 conveyed past the rotating drum 122 so that the micropojections 112 are aligned with the grooves 129. In this embodiment, the micropojections 112 must be aligned in discrete rows, so that each row is conveyed through a separate groove 129.

10 [00051] The micropojection member coating apparatus 130 shown in FIG. 11 is similar to the coating apparatus shown in FIG. 5 with the following differences. A fountain roller 131 brings the coating liquid 132 up to an anilox roller 134. The excess solution is wiped off the anilox roller 134 by a first doctor blade 135. The excess solution is then returned to the container 133. The 15 anilox roller 134 meters the amount of solution transferred to the drum 136. The solution is carried by the drum 136 up to the coating transfer region 137 where it is coated onto the tips of the micropojections. The excess solution is removed from the drum 136 by means of a second doctor blade 138. The dimpled surface of the anilox roller 134 is best shown in FIG. 12. The dimples or cells 20 140 are equal in size and equally spaced on the surface of the anilox roller.

[00052] The coating liquids used in the present invention are typically solutions or suspensions of the pharmacologically active agent, most typically aqueous solutions or suspensions. The coating liquids preferably have a 25 viscosity of about 5 to 500 centipoise (cP), and more preferably about 20 to 50 cP, when measured at a temperature of 25°C and a shear strain rate of 100 sec⁻¹, in order to effectively coat the tiny stratum corneum-piercing elements to an appropriate thickness. The desired thickness of the solid coating on the micropojections is dependent upon the density of the micropojections per unit 30 area and the viscosity and concentration of the coating composition as well as the coating method chosen. In general, coating thickness must be less than 50 µm since thicker coatings have a tendency to slough off the micropojections

upon stratum corneum piercing. Preferred coating thicknesses are less than 10 micrometers as measured from the microprojection surface. Generally coating thickness is referred to as an average coating thickness measured over the coated microprojection. More preferred coating thicknesses are about 0.1 to 10 5 micrometers.

[00053] The kinetics of the agent-containing coating dissolution and release will depend on many factors including the nature of the agent, the coating process, the coating thickness and the coating composition (e.g., the presence 10 of coating formulation additives). Depending on the release kinetics profile, it may be necessary to maintain the coated microprojections in piercing relation with the skin for extended periods of time (e.g., up to about 8 hours). This can be accomplished by anchoring the microprojection member to the skin using adhesives or by using anchored microprojections such as described in WO 15 97/48440.

[00054] The apparatus and method of the present invention have particular utility with coating high potency agents requiring a dose of about 1 mg or less, preferably about 0.25 mg or less. Amounts within this range can be coated onto 20 a microprojection array of the type shown in FIG. 1 having the sheet 12 with an area of up to 10 cm² and a microprojection density of up to 500 microprojections per cm² of the sheet.

[00055] Preferred drugs include desmopressin, luteinizing hormone 25 releasing hormone (LHRH) and LHRH analogs (e.g., goserelin, leuprolide, buserelin, triptorelin), PTH, calcitonin, vasopressin, deamino [Val4, D-Arg8] arginine vasopressin, interferon alpha, interferon beta, interferon gamma, menotropins (urofollotropin (FSH) and leutinizing hormone (LH), erythropoietin (EPO), GM-CSF, G-CSF, IL-10, and glucagon. Preferred vaccines include 30 vaccines for Lyme disease, influenza, hepatitis, hemophilus influenza B, tetanus, typhoid, mumps, measles, rubella, and pertusis.

[00056] In all cases, following coating, the coating solution is dried onto the microprojections by various means. In a preferred embodiment the coated device is dried in ambient room conditions. However, various temperatures and humidity levels can be used to dry the coating solution onto the microprojections.

5 Additionally, the devices can be heated, lyophilized, freeze dried or similar techniques used to remove the water from the coating.

[00057] Other known formulation adjuvants can be added to the coating solution as long as they do not adversely affect the necessary solubility and
10 viscosity characteristics of the coating solution and the physical integrity of the dried coating.

[00058] The following examples are given to enable those skilled in the art to more clearly understand and practice the present invention. They should not
15 be considered as limiting the scope of the invention but merely as being illustrated as representative thereof.

Example 1

20 **[00059]** A 31.0% (w/v) aqueous solution of ovalbumin was prepared by mixing for 1 hour 6.2 grams of ovalbumin (from chicken eggs, crystallized and lyophilized, salt free, sold by Sigma Chemical Co., St. Louis, MO) with 13.8 mL of sterile water. A 1.5 % (w/v) aqueous solution of hydroxyethyl cellulose was prepared by mixing for 1 hour 0.15 g of the hydroxyethyl cellulose with 9.85 mL
25 of sterile water. In a container were added, 6.65 mL of the ovalbumin solution, 1.40 mL of the hydroxyethyl cellulose solution, 0.26 mL of a 0.2M aqueous solution of fluorescein (a fluorescent dye used to make the coating solution, and the resultant dried coating, fluorescent) and 2.0 mL of sterile water and mixed for 1 hour. The resulting 20% ovalbumin, 0.2% hydroxyethyl cellulose, 0.005 M
30 fluorescein solution had a viscosity of about 22 cP at a temperature of 25°C and a rate of shearing strain of 100 sec⁻¹.

[00060] The coating of the microprojection arrays was done using an apparatus similar to that illustrated in FIG. 3. The rotating drum had a diameter of 3.78 cm (1.49 inches). The drum was used with a coating liquid container in the form of a cylindrical trough having a diameter of 4.06 cm (1.6 inches). The 5 drum was driven by an electric motor to turn at a rotational speed of about 2 rpm and a drum surface speed of about 23.8 cm/minute (9.36 inches/minute). The track was adjusted relative to the drum so that the sled cleared the top of the rotating drum by 0.30 mm (0.012 inches). The doctor blade was positioned so that its knife edge was spaced 0.30 mm (0.012 inches) from the drum's surface.

10 3 mL of the coating solution was added to the coating liquid container.

[00061] The microprojection arrays were in the form of etched and punched titanium foils, the foils having a thickness of 30 μm , a width of 2.7 cm (1.07 inches) and a length of 11.5 cm (4.54 inches). The microprojections had a 15 triangular shape (60° tip angle) and a length (measured from the surface of the foil sheet to the tip of the bent triangularly-shaped microprojections) of 250 μm (0.010 inches). The arrays were attached to a sled, oriented so that the microprojections were extending away from the sled and toward the rotating drum, by means of a partial vacuum applied through openings in the side of the 20 sled facing the rotating drum. A partial vacuum of about 0.84 atm (25 inches Hg) was applied.

[00062] The sled was propelled along the track by a spur gear mounted on the same shaft as the drum. The gear engaged a rack on the sled. The gear 25 governed the speed of the sled along the track which was 23.9 cm/minute (9.42 inches /minute).

[00063] The microprojections extending from the sheet of the microprojection array were coated to a depth of approximately 100 μm (0.004 30 inches). Because the coating contained fluorescein dye, the coating depth was measured using a microscope having a lamp emitting light in the UV range.

Example 2

[00064] Coating experiments were performed using the device shown in Fig. 3 and described herein. Increased amounts of a model drug (sucrose) 5 coated on the microprojection array was observed as a function of coating time. The coating solution was an aqueous solution containing 50 wt% sucrose as a model drug and had an initial volume of 2 mL. The microprojection arrays being coated were in the form of a circular metal sheet having an area of 2 cm². The microprojection arrays were composed of titanium, had microprojection lengths 10 of 250 μ m, and a microprojection density of 321 microprojections/cm². The microprojections were tip coated in varying temperature and humidity conditions during operation of the coating device. Coatings were performed continuously for 70 minutes. The sucrose concentration in the coating solution was measured every 10 minutes. The results of the coating solution concentration vs. time are 15 plotted in Fig. 14. The amount of sucrose coated per array was measured and plotted as a function of time in Fig. 15.

[00065] In the first study, coating was conducted at ambient conditions (21 °C, 42% relative humidity). As shown in Fig. 14, there was an increase in 20 sucrose concentration in the coating solution as a function of time during operation of the coating device. Analysis of the dried coatings on the microprojection tips revealed that the amount of sucrose coated increased as a function of time in ambient conditions (see Fig. 15).

25 [00066] In the second study, coating was conducted at 5 °C and 65% relative humidity. This resulted in stable sucrose concentration during the entire duration (70 min) of the coating experiment (see Fig. 14). Analysis of the dried coatings on the microprojection tips revealed that the amount of sucrose coated was constant in cold and higher relative humidity conditions (see Fig. 15).

30

[00067] This experiment demonstrated that significant water evaporation was taking place in ambient conditions and that this could be minimized by

conducting the coating process at lower temperature and/or higher relative humidity than in ambient conditions. Alternatively, the coating process can be conducted using a chilled coating liquid to limit evaporative loss.

5 [00068] In a third study at ambient conditions (21°C, 42% relative humidity), the increase in sucrose concentration as a function of coating time was minimized by constant infusion of 7µL/min water (this water infusion rate had been calculated from the increase in sucrose concentration) into the coating solution. The results are shown in Fig. 16. Overall, these experiments

10 demonstrate that the evolution of the coating solution is linked to evaporation of water from the coating solution. This increase in concentration is detrimental to coating reproducibility that is desirable for pharmaceutical products. This negative effect can be minimized by performing the coating process at lower temperature, at increased relative humidity, by injection of solvent (water) in the

15 drug coating solution reservoir, and/or combinations thereof, to compensate for the solvent evaporation.

Example 3

20 [00069] Coating experiments were performed with several drugs and model compounds using the coating apparatus shown in Fig. 3 and described herein.

[00070] Microprojection arrays were coated in cold conditions with the protein human growth hormone (hGH). Microprojection arrays (titanium sheets, 25 micropjection lengths of 250 µm, micropjection density of 321 micropjections/cm², 2 cm² disc) were tip coated at 5 °C and 65% relative humidity using a 1.7 mL volume of a 20 wt% hGH, 20 wt% sucrose coating solution. Following one coating, analysis revealed that each array was coated with $3.3 \pm 0.2 \mu\text{g}$ hGH. A similar coating experiment was performed except that 30 the microprojection arrays were coated four times with a cycle time of 5 seconds (i.e., each array was coated every five seconds). Analysis revealed that each array was coated with $9.5 \pm 0.9 \mu\text{g}$ hGH (Fig. 17). Scanning electron microscopy

(SEM) of the arrays coated once and four times revealed good uniformity of coating from microprojection to microprojection with the coating limited to the tip (i.e., to the leading 120 μm) of the entire 250 μm microprojection length. This experiment demonstrated that multiple coatings could be used to increase the 5 drug loading on the microprojection array.

[00071] Additional work was performed with the model protein ovalbumin (OVA) in order to evaluate the effect of multiple coating cycles in ambient conditions. Microprojection arrays (titanium sheets, microprojection lengths of 10 250 μm , microprojection density of 321 microprojections/cm², 2 cm² disc) were tip coated at 21 °C and 46% relative humidity using a 2 mL volume of a 20 wt% OVA aqueous coating solution. Microprojection arrays were coated 1, 2 or 4 times with a coating cycle of 5 seconds. Like in the previous experiment, increased coating amounts were obtained with an increase in the number of 15 coatings (see Fig. 18). Also, SEM of the arrays revealed good uniformity of coating from microprojection to microprojection with the coating limited to the leading 120 μm tips of the microprojections.

[00072] Additional work was performed with the peptide growth hormone 20 releasing factor analog (GRF) in order to evaluate the need for intermediate drying between cycles in ambient conditions. Microprojection arrays (titanium sheets, microprojection lengths of 200 μm , microprojection density of 321 microprojections/cm², 2 cm² disc) were tip coated at 21 °C and 46% relative humidity using the coating apparatus shown in Fig. 3 and described herein using 25 1.5 mL of a 7.5 wt% GRF aqueous coating solution. Microprojection arrays were coated 4, 8 or 12 times with coating cycles of 5 and 30 seconds (12 coatings were performed in 1 minute and 6 minutes with 5 second and 30 second coating cycles, respectively). Analysis of the microprojection arrays (5 arrays per condition) demonstrated good reproducibility of coating in all conditions with a 30 trend toward decreased variability with increased number of coatings. The amount of GRF increased with the number of coatings with both coating cycle times. Higher coating levels were obtained with the longer coating cycle but the

effect was surprisingly small (see Fig. 19). SEM of the arrays revealed good uniformity of coating from microprojection to microprojection with the coating limited to the leading 120 μm tips of the microprojections.

5 [00073] Overall, these experiments demonstrate that the coating cycle time can be shorten to as low as 5 seconds, which improves manufacturing.

Claims:

1. A method of coating a liquid onto a plurality of microprojections (12, 112) extending from a surface or edge of a substrate (14) substantially without coating the liquid onto the substrate (14) comprising:
 - 5 providing an agent-containing coating liquid (24, 124);
 - conveying the coating liquid onto a liquid-holding surface (23, 73, 129, 136) having a coating transfer region (25, 75, 125, 137);
 - controlling the depth of the coating liquid at the coating transfer region to a predetermined depth; and
 - 10 immersing the microprojections to a predetermined level in the coating liquid at the coating transfer region.
2. The method of claim 1, wherein the microprojections (12) have a length, as measured from a surface or edge of the substrate (14), which is greater than 15 said predetermined depth.
3. The method of claim 2, wherein the depth of the coating liquid at the coating transfer region is greater than said microprojection immersion.
- 20 4. The method of claim 1, wherein the liquid-holding surface is a surface of a roller (22, 52).
5. The method of claim 4, wherein the conveying of the coating liquid is achieved by rotating a portion of the roller (22) through a bath (24) of the coating liquid. 25
6. The method of claim 5, wherein the depth of the coating liquid is controlled by controlling the rotational speed of the roller (22).
- 30 7. The method of claim 1, wherein the immersing of the microprojections is accomplished by conveying the substrate (14,42) along a predetermined pathway (32,44) adjacent the coating transfer region (25).

8. The method of claim 7, wherein a web (42) comprised of a plurality of said substrates (10a, 10b, 10c) is conveyed continuously along the predetermined pathway (44).

5

9. A method of forming a solid coating (18) on a plurality of microprojections (12) extending from a surface or edge of a substrate (14) substantially without forming a coating on the substrate, comprising the method of claim 1 and including:

10. removing the microprojections (12) from the coating liquid (24); and
drying the coating liquid coating the microprojections thereby forming a solid agent-containing coating (18) on the microprojections (12).

11. The method of claim 9, including repeating said coating, removing and
drying to provide multiple coatings on said microprojections.

12. The method of claim 9, wherein the agent is a drug or a vaccine and the liquid comprises water.

13. The method of claim 9, wherein the coating liquid is comprised of a liquid solvent and the agent, the coating liquid having an agent concentration, and said agent concentration is controlled by a method selected from the group consisting of:

- i) conducting said coating at an atmospheric temperature which reduces evaporative loss of said liquid solvent;
- ii) conducting said coating using a coating liquid having a temperature which reduces evaporative loss of said liquid solvent;
- iii) conducting said coating in an atmosphere containing sufficiently high amounts of gaseous solvent to reduce evaporative loss of said liquid solvent;
- iv) infusing liquid solvent into said coating liquid at a rate which

compensates for evaporative loss of said liquid solvent; and
v) combinations thereof.

13. The method of claim 12, wherein the liquid solvent comprises water, the
5 temperature is less than about 10°C, and the atmosphere has a relative humidity
greater than about 60%.

14. An apparatus for coating an agent-containing liquid onto a plurality of
micropressions (12) extending from a surface or edge of a substrate (14)
10 substantially without coating the substrate, comprising:

a liquid holding surface (23, 73) having a coating transfer region (25, 75);
a coating liquid conveyor (22) for providing the coating liquid (24) at the
coating transfer region (25);
a coating liquid depth controller (28) for controlling the depth of the
15 coating liquid at the coating transfer region to a predetermined depth; and
a substrate conveyor (30, 32, 34) for conveying the micropressions (10,
12) at a predetermined level of immersion through the coating liquid at the
coating transfer region (25).

20 15. The apparatus of claim 14, wherein the liquid holding surface (23) is
curved.

16. The apparatus of claim 15, wherein the liquid holding surface is an outer
surface of a rotatable cylindrically-shaped roller (22, 52).

25 17. The apparatus of claim 16, wherein the coating liquid conveyor comprises
rotating the roller (22, 52) through a bath (24, 26) of said coating liquid.

18. The apparatus of claim 17, wherein the coating liquid depth controller
30 comprises a doctor blade (28).

19. The apparatus of claim 17, wherein the coating liquid depth controller

comprises a second roller (54), substantially parallel with the liquid holding surface roller (52) and spaced a predetermined distance therefrom forming a nip therebetween.

5 20. The apparatus of claim 19, wherein the two rollers (52, 54) rotate in the same rotational direction.

21. The apparatus of claim 19, including a doctor blade (56) wiping the surface of the second roller upstream of the nip.

10

22. The apparatus of claim 14, wherein the liquid holding surface (73) is immobile.

23. The apparatus of claim 22, wherein the coating liquid conveyor (72) 15 causes the coating liquid (74) to flow, by force of gravity, over the immobile liquid holding surface (73).

24. The apparatus of claim 23, wherein the immobile liquid holding surface (73), in the coating transfer region (75), is substantially planar.

20

25. The apparatus of claim 23, wherein the immobile liquid holding surface, in the coating transfer region, is curved.

25

26. The apparatus of claim 25, wherein the curved surface is cylindrical.

27. The apparatus of claim 14, wherein the substrate conveyor (30) comprises a track (32) which is adjustably positionable to a predetermined distance from the coating transfer region (25) and a substrate holding sled (34) which runs along the track (32).

30

28. The apparatus of claim 14, including a continuous substrate conveyor (40) for continuously conveying a series of said substrates and microprojections (10a,

10b, 10c) through the coating liquid.

29. The apparatus of claim 28, wherein the continuous substrate conveyor comprises a substrate supply roll (46) and a substrate take-up roll (48).

5

30. The apparatus of claim 29, further including a substrate guide (44) for positioning the continuous substrate (42) relative to the coating transfer region (25).

10 31. The apparatus of claim 14, wherein the coating liquid is comprised of a liquid solvent and the agent, the coating liquid having an agent concentration, and means for controlling said agent concentration selected from the group consisting of;

- 15 i) a temperature controller for controlling the atmospheric temperature around said coating to a level which reduces evaporative loss of said liquid solvent;
- ii) a temperature controller for controlling the temperature of said coating liquid to a level which reduces evaporative loss of said liquid solvent;
- 20 iii) a coating atmosphere controller for controlling levels of gaseous solvent in an atmosphere surrounding said coating which reduces evaporative loss of said liquid solvent;
- iv) a liquid solvent infusor for infusing liquid solvent into said coating liquid at a rate which compensates for evaporative loss of said liquid solvent; and
- 25 v) combinations thereof.

32. The apparatus of claim 31, wherein the liquid solvent comprises water, the temperature is less than about 10°C, and the atmosphere has a relative humidity greater than about 60%.

1/9

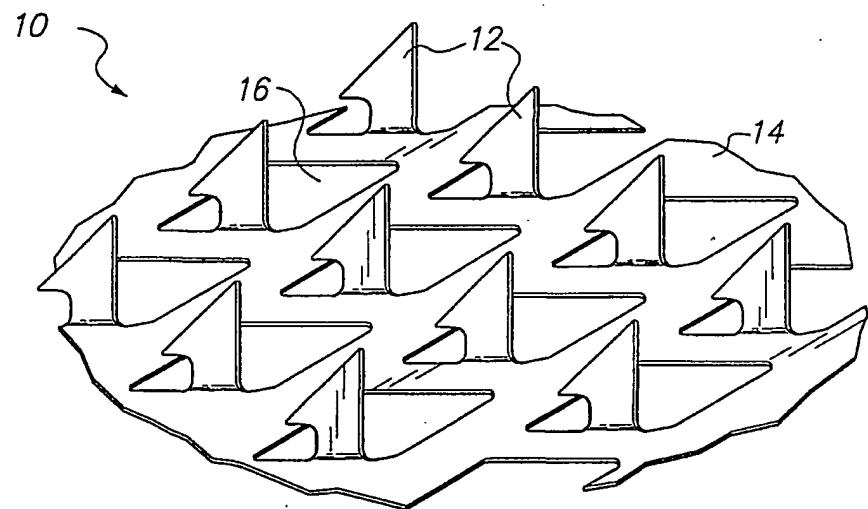


FIG. 1

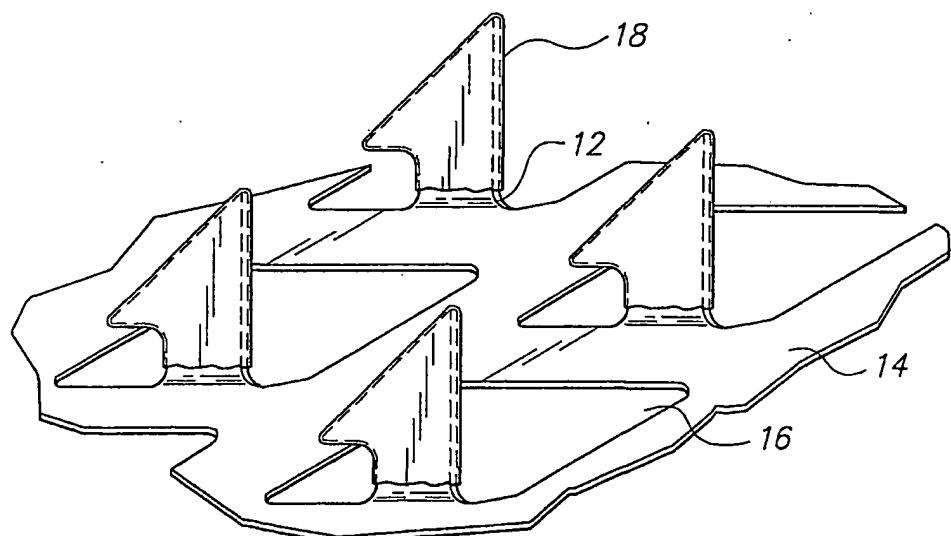


FIG. 2

2/9

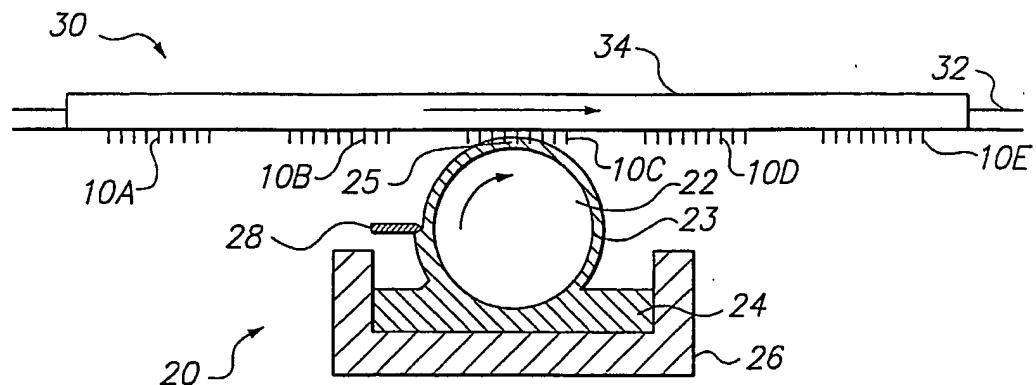


FIG. 3

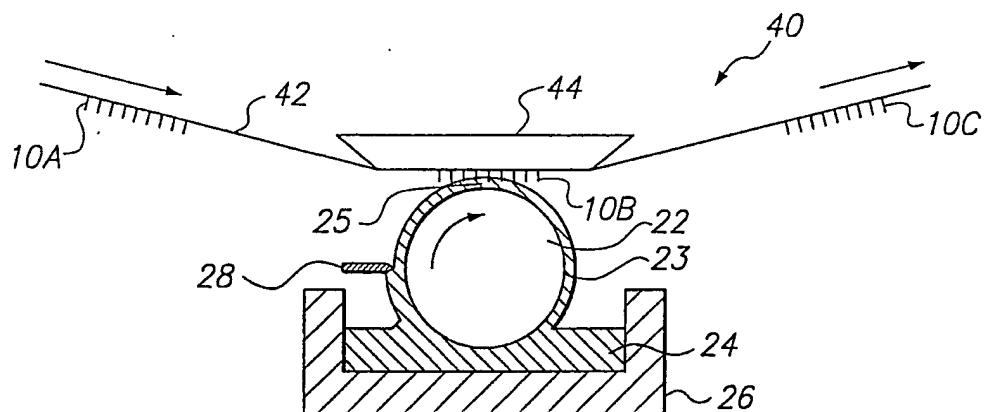


FIG. 4

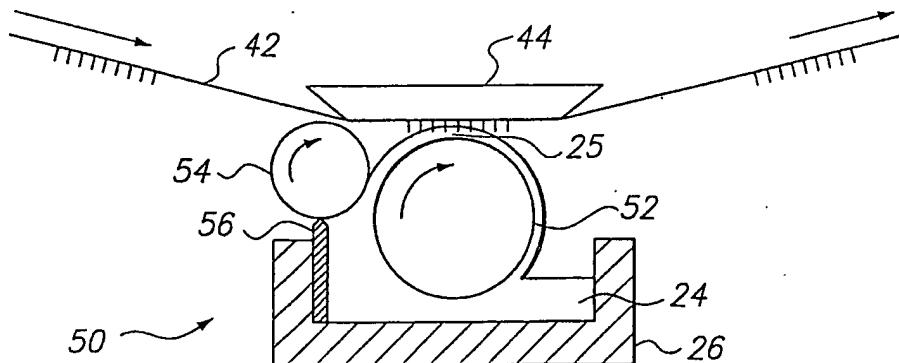


FIG. 5

3/9

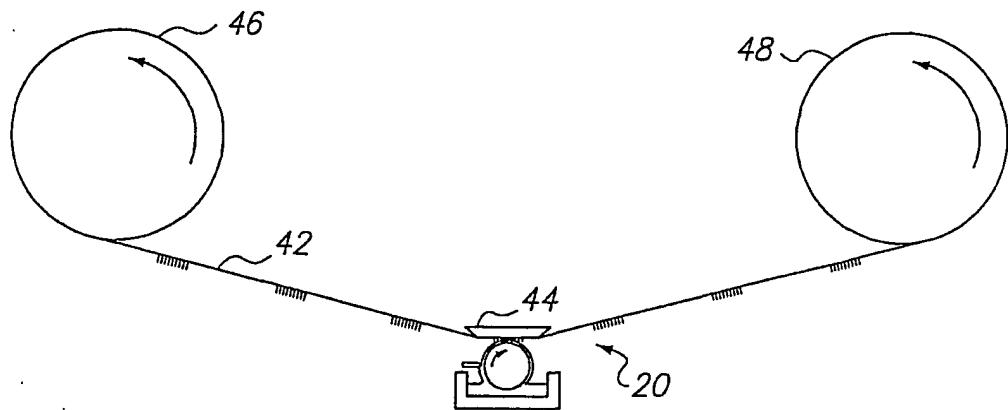


FIG. 6

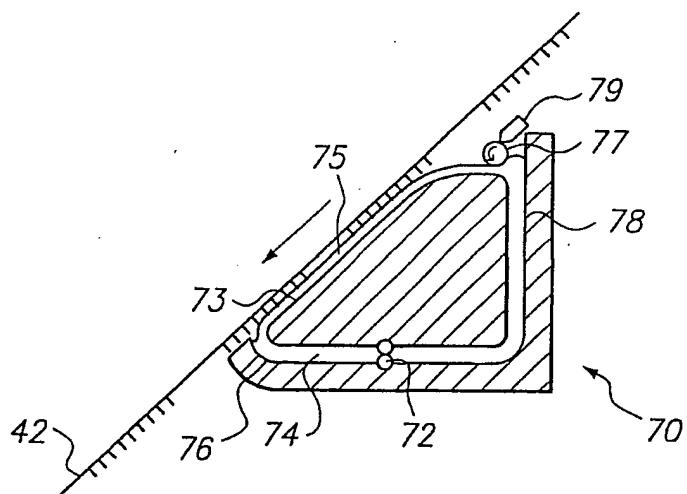


FIG. 7

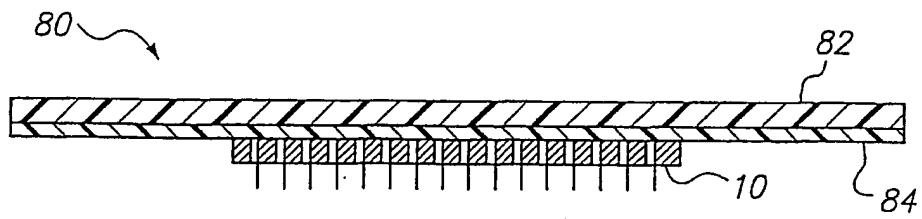
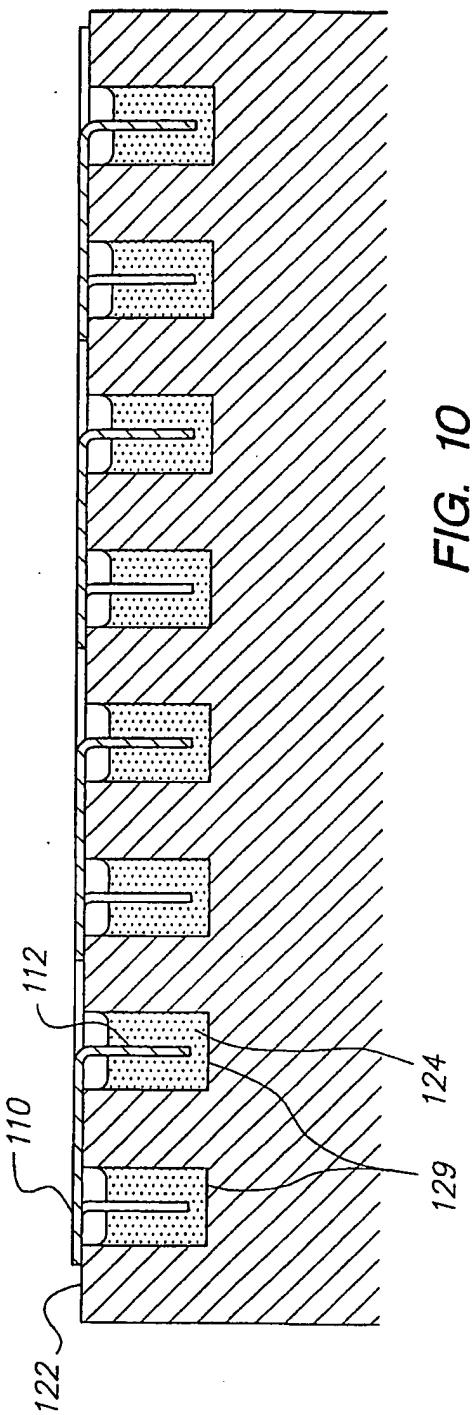
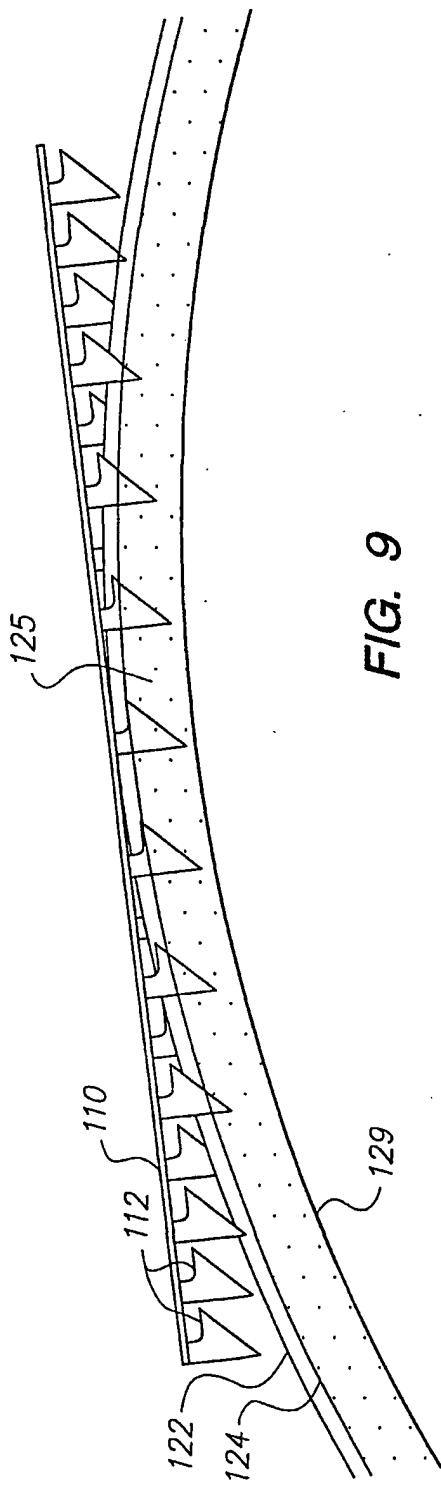
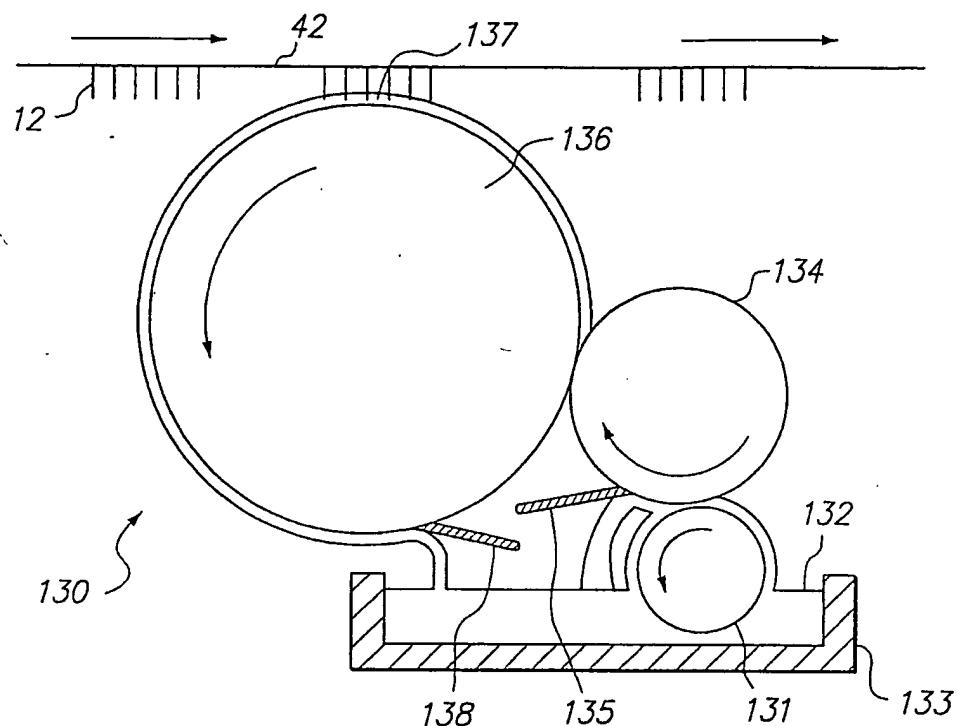
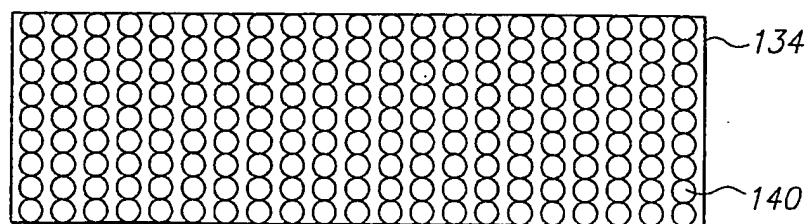


FIG. 8

4/9



5/9

**FIG. 11****FIG. 12**

6/9

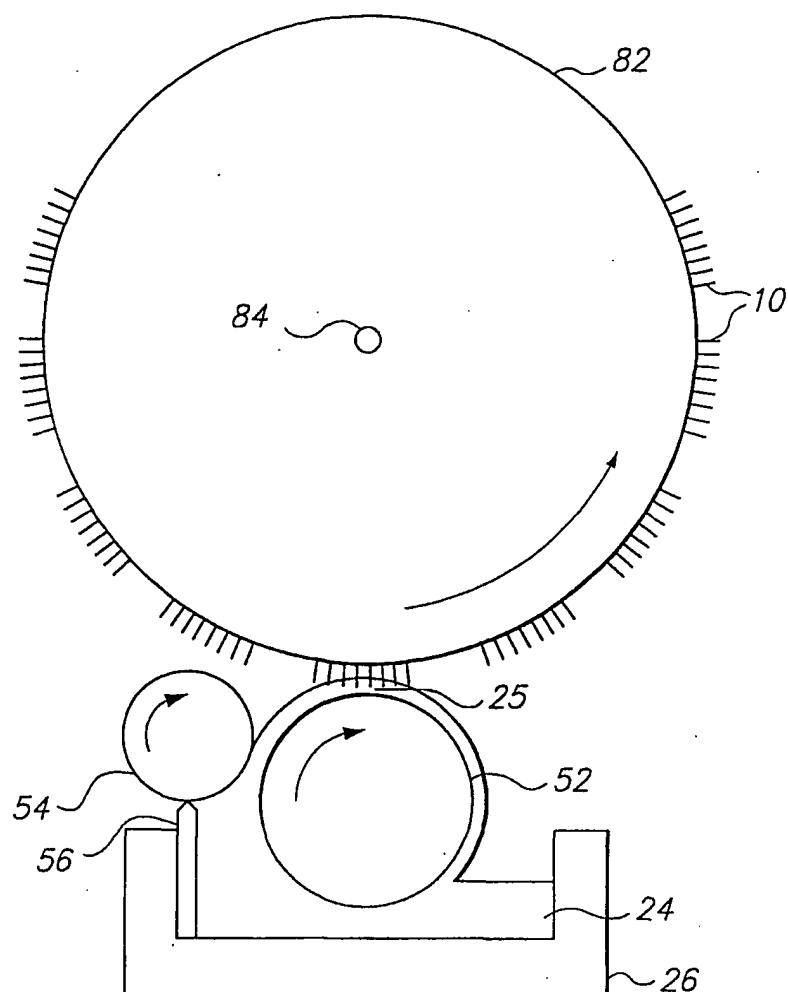


FIG. 13

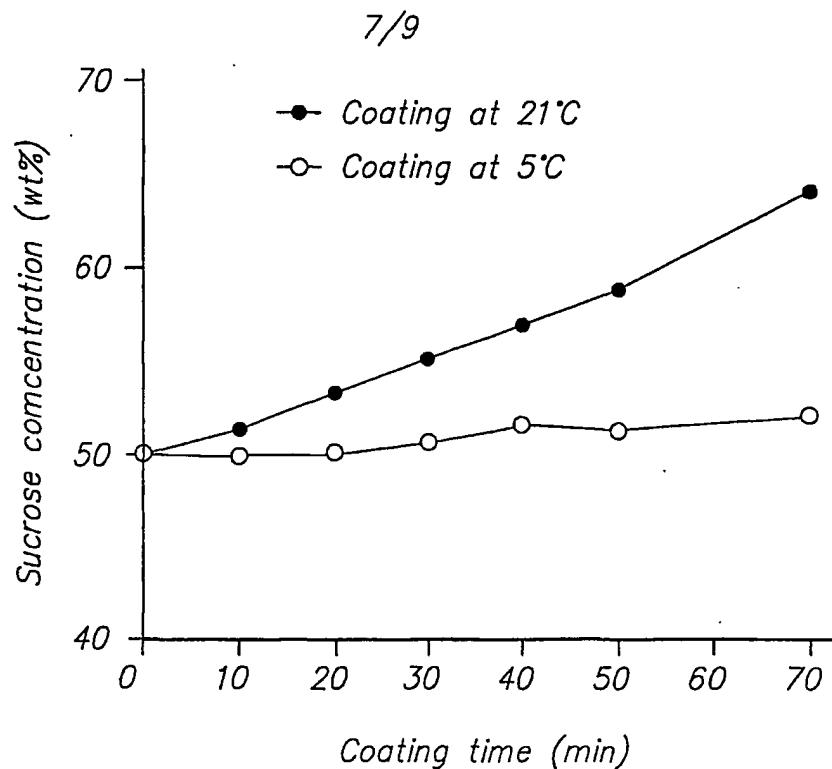


FIG. 14

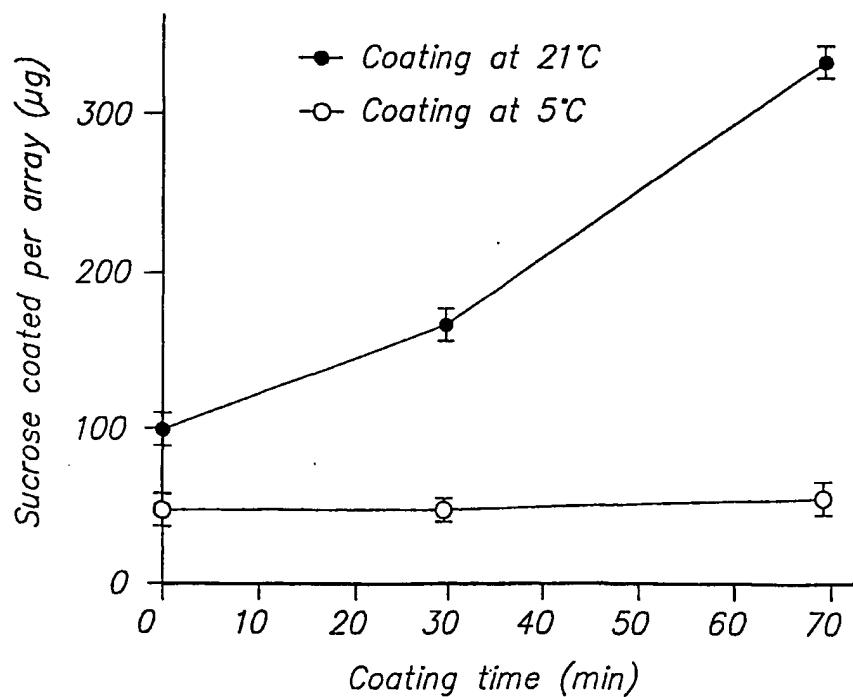


FIG. 15

8/9

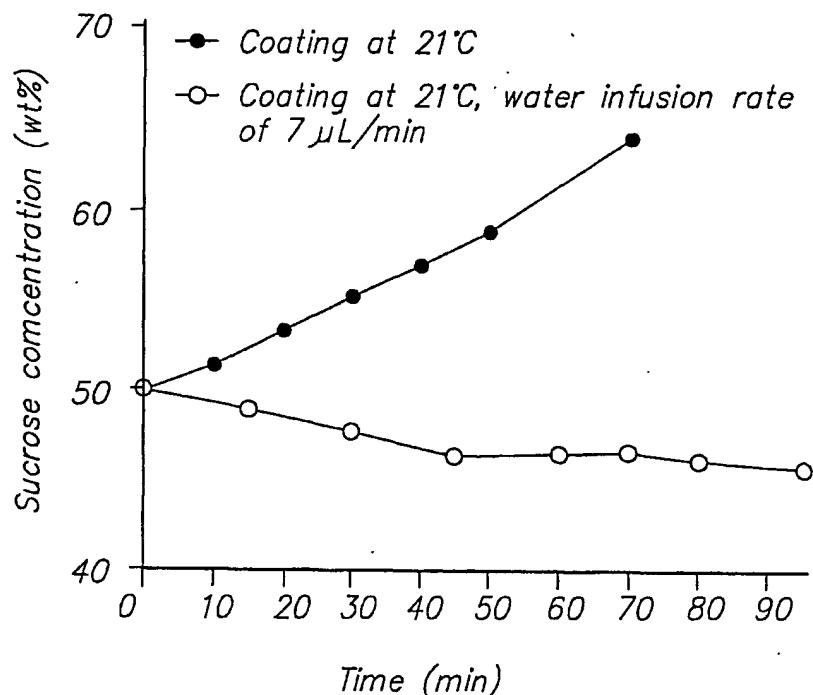


FIG. 16

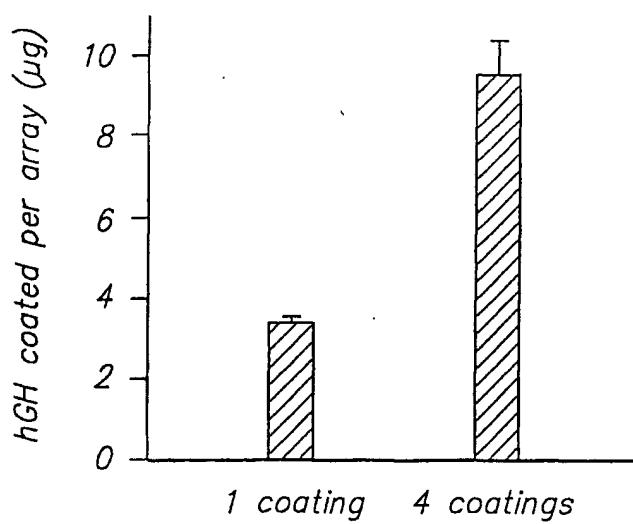


FIG. 17

9/9

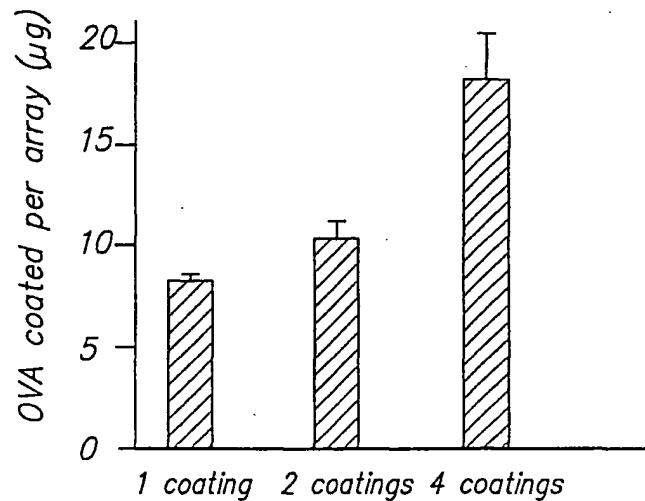


FIG. 18

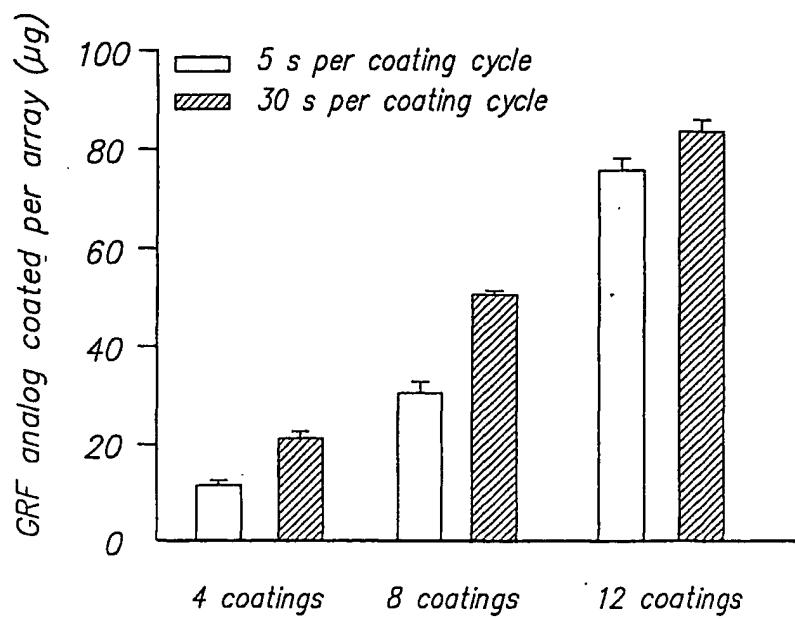


FIG. 19

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/07674

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61B17/20 B05D1/18 B05D1/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61B B05D A61K A61H G01S

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 353 942 A (CAREY RICHARD D) 12 October 1982 (1982-10-12) column 1, line 15 - line 17; figures 1,3 column 1, line 56 -column 2, line 9 column 2, line 61 -column 3, line 16 column 3, line 54 -column 4, line 21 column 4, line 50 - line 63 column 5, line 14 -column 6, line 5 column 5, line 50 - line 53 ---	1-10,12, 14-17, 22-25, 27,28,31
Y	-/-	11

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search 3 July 2002	Date of mailing of the international search report 22/07/2002
Name and mailing address of the ISA European Patent Office, P.B. 5018 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Brumme, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/07674

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 510 933 A (TAYLOR ARTHUR S ET AL) 12 May 1970 (1970-05-12) column 1, line 30 - line 31 column 2, line 30 - line 33 column 5, line 78 -column 6, line 3 column 6, line 35 - line 44; figures 1-20 column 6, line 69 - line 73; claims 1-21 column 6, line 26 - line 30; figures 9-14 ---	1-3, 7-9, 14, 23, 24, 27-30
Y	---	11, 15, 25, 26
X	US 5 671 753 A (PITESKY ISADORE) 30 September 1997 (1997-09-30) column 3, line 38-54; figures 1,2 column 34, line 23 - line 42 column 5, line 23 - line 50 column 4, line 23 - line 47; figure 1 ---	1-3, 14, 22-24
Y	---	15, 25, 26
A	US 4 657 783 A (TATT CHRISTOPHER F ET AL) 14 April 1987 (1987-04-14) the whole document ---	13, 18-21, 29, 30, 32
A	US 2 345 070 A (EDWARD POWELL) 28 March 1944 (1944-03-28) column 1, line 5 - line 16 column 1, line 49 -column 3, line 36 ---	1-3, 14
A	US 3 470 011 A (UHL HERBERT BENNETT ET AL) 30 September 1969 (1969-09-30) the whole document -----	1-3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/07674

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
US 4353942	A	12-10-1982	CA	1197419 A1		03-12-1985
US 3510933	A	12-05-1970	NONE			
US 5671753	A	30-09-1997	NONE			
US 4657783	A	14-04-1987	DE EP FI JP JP JP	3560072 D1 0153029 A1 850314 A ,B, 1050464 B 1667403 C 60179168 A		02-04-1987 28-08-1985 28-07-1985 30-10-1989 29-05-1992 13-09-1985
US 2345070	A	28-03-1944	NONE			
US 3470011	A	30-09-1969	NONE			